HHS Public Access

Author manuscript

Muscle Nerve. Author manuscript; available in PMC 2015 June 26.

Published in final edited form as:

Muscle Nerve. 2014 June ; 49(6): 814–821. doi:10.1002/mus.24078.

SIBLING CONCORDANCE FOR CLINICAL FEATURES OF DUCHENNE AND BECKER MUSCULAR DYSTROPHIES

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Abstract

Introduction—The correlation of markers of disease severity among brothers with Duchenne or Becker muscular dystrophy has implications for clinical guidance and clinical trials.

Methods—Sibling pairs with Duchenne or Becker muscular dystrophy (n = 60) were compared for ages when they reached clinical milestones of disease progression, including ceased ambulation, scoliosis of ≥ 20°, and development of cardiomyopathy.

Results—The median age at which younger brothers reached each milestone, compared with their older brothers ranged from 25 months younger for development of cardiomyopathy to 2 months older for ceased ambulation. For each additional month of ambulation by the older brother, the hazard of ceased ambulation by the younger brother decreased by 4%.

Conclusions—The ages when siblings reach clinical milestones of disease vary widely between siblings. However, the time to ceased ambulation for older brothers predicts the time to ceased ambulation for their younger brothers.

Keywords

ambulation; Becker muscular dystrophy; cardiomyopathy; Duchenne muscular dystrophy; scoliosis; sibling features

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Duchenne and Becker muscular dystrophy (DBMD) may occur in multiple sons within a family and is associated with variable manifestations among brothers. Common medical complications include loss of ambulation, scoliosis, and cardiomyopathy. The life expectancy of boys with DBMD has improved from 14.4 years in the 1960s to 25.3 years in the 1990s, as more effective treatments have evolved, particularly the use of corticosteroids to preserve muscle function and improved respiratory management to prevent pulmonary complications.[1,2] With increased life expectancy, more boys will experience complications associated with advanced disease, including increased use of mobility aids and treatment for scoliosis and cardiomyopathy. The mean ages for onset of these clinical milestones of disease progression have been published[3–8] and can serve as a rough prognostic guide for newly diagnosed individuals.

For families with more than 1 affected son, parents and medical providers may question how similar their clinical courses will be. For investigators in DBMD, the similarities and differences among siblings may also be important for studying the influence of modifying genes or the effects of new treatments on clinical outcomes. The purpose of this report is to use data from the Muscular Dystrophy Surveillance Tracking and Research Network (MD STAR*net*), a population-based public health surveillance program, to investigate the degree of concordance among siblings with DBMD for age at onset of key clinical milestones of disease progression. This information has important implications for prognostic counseling and anticipatory guidance in families with multiple affected siblings.

MATERIALS AND METHODS

The MD STAR*net* is a multi-site, population-based surveillance system that collects extensive medical information on boys with DBMD born since January 1, 1982 in Arizona, Colorado, Georgia, Iowa, and western New York. MD STAR*net* collects pertinent and available information in patient records from regional neuromuscular clinics, hospitals, outpatient clinics, death certificates, hospital discharge databases, and other medical sources. The study population includes boys with a clinical diagnosis from a neurologist of Duchenne or Becker muscular dystrophy, characteristic signs and symptoms, an elevated creatine kinase level, a documented dystrophin mutation, a muscle biopsy demonstrating abnormal dystrophin by immunostaining or Western blot, and/or a positive family history of an X-linked muscular dystrophy. A full description of the MD STAR*net* methods has been published.[9] This study was conducted under the approval of human subjects review boards of each participating surveillance site. This analysis includes data collected through September 2011.

Figure 1 depicts criteria for inclusion in the study population. The MD STAR*net* population includes 874 boys with DBMD. Among this population are 60 families with more than 1 affected boy. Seven families included 3 or 4 affected boys, from whom 2 were selected for inclusion. For sibships with more than 2 affected siblings, we chose the 2 siblings with the fewest missing values and included only that pair in analyses of the correlation within pairs for each clinical milestone. If multiple siblings had the same number of missing values, the oldest was chosen for inclusion. Therefore, our final study cohort includes 120 boys from 60 families with multiple affected siblings. The median year of birth was 1992 (range, 1982–

2006), and the median age of study participants at their most recent abstracted medical visit was 16.1 years (range, 3.1 to 26.7 years). The median age difference between pairs of brothers included in the analysis was 3.1 years (range, 0 to 19 years). Four of the pairs are half siblings, and 2 pairs are twins. The zygosity of the twin pairs was not noted in their records.

The clinical milestones examined in the study cohort were: (1) ceased ambulation, (2) scoliosis of 20° or more, and (3) onset of cardiomyopathy. Onset ages for these milestones are reported in years and months. Onset of ceased ambulation was defined as the age when the individual ceased walking or used a wheelchair full time. Onset of scoliosis was defined as the first date that a spine radiograph demonstrated a Cobb angle of ≥ 20°. The degree of curvature was determined from available reports in the medical record and was not measured independently by the authors. Onset of cardiomyopathy was defined as the age that an echocardiogram first identified a fractional shortening (FS) < 28%, or if a measure of FS was not available, an ejection fraction (EF) < 55%. As with scoliosis and ambulation measures, cardiac function was determined through information available in medical record reports and was not assessed independently. Oral corticosteroid use was examined as a potential confounder for each of the outcomes. Boys were defined as corticosteroid users if they took this medication for at least 6 months at any time before reaching the clinical milestone under consideration.

DBMD is a degenerative disorder in which affected individuals progress from normal function to dysfunction over a period of years. In order for a sibling to be considered “at risk” for a clinical milestone, he must have reached an age when clinical onset might be possible. In this study, the minimum risk age for each milestone condition was defined as the youngest documented onset of the condition, as found within the MD STAR*net* population database (n = 874). For our analyses of the relationship of the progression of an older sibling’s condition compared with his younger brother’s progression, the younger sibling must be at an age when he is at risk for the given condition. Therefore, if the younger brother of a sibling pair had not yet reached the minimum risk age for a milestone, the sibpair was excluded from all analyses of that milestone.

Descriptive statistics for continuous variables were calculated as medians and ranges and for categorical variables as frequencies and percentages. Analysis of variance was used to examine whether the age difference between brothers was greater for siblings who were discordant than for siblings who were concordant.

Simple correlation coefficients were not calculated, because they would include only sibling pairs in which both brothers had experienced the milestone, thus biasing the results toward brothers who were more similar (i.e., both have reached the clinical milestone). Instead, we used a Cox proportional hazard model to examine the effect of an older sibling’s milestone onset age on when his younger sibling reached the same milestone or the maximum age at which the younger brother was known to not have reached the milestone. Cox proportional hazard model analysis allowed us to also include sibling pairs in which only the older brother had experienced the milestone and the younger brother had not. Chronological age was measured as a continuous variable, and corticosteroid use was examined as a potential

confounder. The starting time for being at risk for a given condition was defined as the youngest age at which the milestone was met in the full MD STAR*net* database (n=874 males). Because the older brother's milestone onset age was used as the predictor for the Cox proportional hazard analysis, we excluded sibling pairs in which the older brother had not yet experienced the milestone. We also tested models that included 1 of 5 additional steroid confound variables: (1) the use of corticosteroids for at least 6 months before ceased ambulation by the older brother; (2) the use of corticosteroids for at least 6 months before ceased ambulation by the younger brother; (3) the duration of corticosteroid use by the older brother; (4) duration of corticosteroid use by the younger brother; and (5) a categorical variable of whether neither, 1, or both brothers used corticosteroids.

We used Kaplan-Meier survival curves to examine the effect of older brothers reaching these milestones on the probability that their younger brothers would follow a similar clinical course. The median age when older brothers reached each milestone was used to categorize them as "early" or "late," depending on whether they reached that milestone before or after the median age of the analysis sample. The log-rank test was used to determine whether the curve for the early group was different significantly from the curve for the late group.

RESULTS

Among all 120 siblings, the youngest age when each milestone was reached was 5 years, 5 months for cardiomyopathy, 7 years, 0 months for ceased ambulation, and 10 years, 4 months for scoliosis ≥20 °. The minimum risk age for each condition, as determined from the full MD STAR*net* database was 4 years, 9 months for cardiomyopathy, 6 years, 0 months for ceased ambulation, and 6 years, 8 months for scoliosis, as shown in Table 1. The majority of the study population was at least as old as these minimums and, therefore, at some risk of progression by the time of their most recently abstracted visit. Of the younger brothers, 3 were too young to have developed cardiomyopathy, 8 were too young to have ceased ambulation, and 10 were too young to have developed scoliosis.

The number of sibling pairs in which both brothers (concordant progression), 1 brother (discordant progression), or neither brother (concordant nonprogression) reached each milestone is listed in Table 1. Only those sibling pairs who met minimum risk age for that milestone are included. For those sib pairs with concordant progression, the difference between a younger sibling's age at condition onset compared with his older sibling's age at condition onset is listed in Table 2 (median and range).

On average, sibling pairs that were discordant for progression tended to have a greater time gap between the siblings' births. Siblings discordant for ceased ambulation had a significantly greater chronological age difference compared with siblings who were concordant for progression or concordant for nonprogression (t-statistic$_{\text{concordant vs. nonconcordant}}$ = 2.75; P = 0.008). The difference in sibling chronological age was not significant for pairs concordant or discordant for scoliosis (t-statistic = 1.471; P = 0.147) or cardiomyopathy (t-statistic = −0.817, P = 0.417).

Use of corticosteroids for at least 6 months before condition onset, or, for those who did not have onset, 6 months before their most recent visit record was evaluated for its effect on concordance. The median start age of steroid treated individuals was 7 years, 3 months, and the median duration was 2 years, 5 months. In 21 of the 35 sibling pairs concordant for ceased ambulation, neither brother had been treated with corticosteroids for at least 6 months before ceased ambulation. In 9 of these sib pairs, both siblings had been treated with corticosteroids, and in 5 sibling pairs, the older brother had been treated with corticosteroids and the younger had not. Among the sibling pairs concordant for ceased ambulation there were no pairs in which only the younger brother had been treated with corticosteroids for >6 months before ceased ambulation. Similarly, neither brother was treated with corticosteroids in the majority of the concordant sibling pairs before development of scoliosis (6/9) or cardiomyopathy (9/19). Only in a single sibling pair concordant for cardiomyopathy was the younger brother treated with corticosteroids for >6 months before the outcome, while the older brother was not.

Results of the Cox proportional hazard model are shown in Table 3. Among the 3 clinical milestones examined, loss of ambulation was the only milestone for which there was a significant correlation between older and younger brothers. For each additional month of ambulation by the older brother, the hazard of cessation of ambulation by his younger brother decreased by 4%. None of the corticosteroid variables, (1) the use of corticosteroids for at least 6 months before the cessation of ambulation by the older brother, (2) the use of corticosteroids for at least 6 months before cessation of ambulation by the younger brother, (3) the duration of corticosteroid use by the older brother, (4) duration of corticosteroid use by the younger brother, or (5) a categorical variable of whether neither, one, or both brothers used corticosteroids, was significant.

We focused the Kaplan-Meier analysis on ceased ambulation because of the significant correlation between brothers for this clinical milestone by Cox regression. The results of the Kaplan-Meier analysis shown in Figure 2 illustrate the relationship between the proportion of younger brothers still ambulatory and whether their older brothers ceased ambulation early or late. Using the log-rank test, early versus late ceased ambulation for older brothers predicts the time to ceased ambulation for their younger brothers ($P < 0.001$).

The data were examined to determine whether the results of the Cox proportional hazard or the Kaplan-Meier analysis were affected by the presence of half siblings in the study population or by surveillance bias. The 4 sets of half siblings did not affect the results; when the analyses were repeated omitting the half sibling pairs, the results did not change significantly. The results did not change significantly after eliminating the 2 twin pairs, either.

Surveillance bias would be present if a greater number of medical visits increased the likelihood that scoliosis or cardiomyopathy would be detected. The number of visits by each sibling in a pair are correlated (Pearson correlation coefficient 0.774, $P < 0.001$); however, an independent samples *t*-test comparing older brothers with scoliosis to those without scoliosis indicates that the number of visits per month of age before the diagnosis of scoliosis does not differ from the number of visits per month of those without scoliosis ($P =$

0.453), nor is the number of visits before the diagnosis correlated with the age at diagnosis by a Pearson correlation coefficient ($P = 0.116$). Likewise, an independent samples *t*-test comparing older brothers with cardiomyopathy to those without indicates that the number of visits per month of age before the diagnosis of cardiomyopathy does not differ from the number of visits per month of those without cardiomyopathy ($P = 0.878$), nor is the number of visits before the diagnosis correlated with the age at diagnosis by a Pearson correlation coefficient ($P = 0.637$).

DISCUSSION

Individuals with single gene disorders may have highly variable clinical features, even though they share the same mutation. Because siblings share many of the same modifying genes and environmental factors, they are likely to be more phenotypically similar than others with the same mutation. In our main analyses, each older sibling was used as a predictor for one who has the same DBMD mutation (namely, his younger brother). This intrasibling comparison serves to stratify on each individual mutation. If the DBMD mutation alone could entirely explain onset age for clinical milestones, the predictive value of the older brother's onset on his younger brother's onset would indeed be far stronger than we observed.

Birnkrant et al.[10] analyzed pulmonary and cardiac function in sibling pairs with Duchenne and Becker muscular dystrophies and found discordant pulmonary outcome among 3 of 7 pairs and discordant cardiac outcome in 3 of 6. They concluded that this variation could have implications for using genotype information to predict the clinical course of DBMD and response to treatments. The observed variability in expression between brothers with the same mutation underscores this point. Although the clinical outcome of older brothers predicted those of their younger brothers for loss of ambulation, we did not find it to be predictive for development of scoliosis or cardiomyopathy in this dataset with the small sample sizes for these milestones. Furthermore, there were sibships for which the differences in reaching clinical milestones were striking, as much as a 6 year, 9 month difference for ceased ambulation, a 3 year 10 month difference for scoliosis ≥ 20°, and an 11 year 11 month difference for cardiomyopathy. This natural variation in clinical outcome among boys with identical dystrophin gene mutations and similar modifying gene profiles suggests that trials of therapeutic interventions will likely require a large number of subjects to detect a significant effect size.

The wide variation in DBMD expression between siblings with the same mutation may be influenced by many factors, including use of different treatments, medical complications such as obesity, the presence of modifying genes, and epigenetic effects. Use of oral corticosteroids is one such treatment that has been associated with prolonged ambulation and may contribute to siblings being more or less similar.[11–13] We found no significant effect of corticosteroid use on the correlation between brothers' ages when they reached each milestone, although in this dataset the number of siblings being treated with steroids was relatively small, limiting the conclusions that can be drawn from the finding. Though we were unable to measure the effects of modifying genes, at least 1 previous investigation found significant negative effects on both disease progression and response to

corticosteroids in boys with a polymorphism in the promoter region of the *SPP1* (osteopontin) gene.[14] The authors rightly point out that stratification of clinical trials by genotype, including known modifiers, such as the *SPP1* polymorphism, may improve sensitivity and increase statistical power. From a clinical perspective, analysis of modifier genotypes may also improve the accuracy of prognosis estimates and might lead to timelier introduction of health surveillance maneuvers and treatments. Variation in clinical outcome has also been observed in siblings with substantial differences in expression of genes believed to be responsible for control of the cell cycle and other processes such as cellular proliferation and differentiation.[15] Gene loci that are underexpressed or over-expressed in patients with mild phenotypes are potential targets for treatments that alter the expression of these genes and result in improved outcomes. Studies of discordant sibling pairs may be particularly useful for identifying these candidate genes.

Perhaps the most critical, and certainly the most studied complication of DBMD is the progressive loss of independent ambulation. Loss of ambulation has been used to distinguish dystrophinopathy phenotypes, with boys who cease to walk before age 13 years being classified as having Duchenne muscular dystrophy, those who cease to walk after age 16 years being classified as Becker muscular dystrophy, and those who cease to walk between ages 13 and 16 years having an intermediate phenotype. The median age of cessation usually occurs between ages 9 and 11 years for those with the Duchenne phenotype.[1,7,11,12] In our investigation, among the 35 sibling pairs for which both members had ceased ambulation, the median age of ceased ambulation was 10 years, 7 months (95% CI 9.1,12.1), and the age when the older brother ceased ambulation was a significant predictor for age ambulation ceased for his younger sibling. Among sibships concordant for progression, the median age of ceased ambulation for younger brothers was approximately 2 years, 1.5 months later among those whose older brothers ceased ambulation late compared with those whose older brothers ceased ambulation early. Although brothers ceased ambulation within 1 year, 6 months of one another in 50% of sibling pairs concordant for ceased ambulation, the differences in age at ceased ambulation were substantial for other brothers, as high as 6 years, 9 months. Nonetheless, these data provide a general estimate of the degree to which younger siblings will follow a clinical course that is similar to their older brothers. Corticosteroid treatment is associated with improved muscle strength, function, and prolonged ambulation[11–13] and might be expected to influence concordance if: (1) 1 brother uses corticosteroids but the other does not; or (2) there is a difference in duration of corticosteroid use between 2 brothers who both use corticosteroids. In this analysis, however, we found no significant effect of corticosteroid use on ceased ambulation in either circumstance. The reason we did not observe such a treatment effect is most likely the result of small numbers of sibling pairs (n = 20) in which 1 or both brothers used corticosteroids.

As postural muscle strength decreases in boys with DMD they develop scoliosis, and it advances more rapidly after they cease ambulation.[13] Of the 33 sibling pairs who had at least 1 sibling progress to scoliosis, only 9 sibling pairs had both who developed scoliosis. Among the pairs in which the older brother had progressed (n = 29), the older brothers' age of scoliosis did not predict when this condition appeared in the younger brothers. Furthermore, in 27 sibling pairs, neither brother had developed scoliosis, despite the fact that

most of the boys had ceased ambulation. These data suggest that additional investigation is warranted regarding the relationship between scoliosis and ambulation status, to identify possible predisposing and protective factors.

Cardiomyopathy occurs commonly in boys with DBMD, and the great majority show echocardiographic signs of dysfunction by age 18 years.[16,17] In our study there was a median difference of 2 years, 1 month in cardiomyopathy onset between brothers in 19 sibling pairs who were concordant for development of cardiomyopathy, and the age of cardiomyopathy onset in older brothers did not predict age of onset for younger brothers. Although an individualized cardiomyopathy surveillance strategy that considers family history and mutation type might be desirable, our data suggest that these factors do not provide sufficient predictive power to support such a strategy.

One of the primary strengths of this analysis is that it is drawn from a population-based sample, rather than a clinical referral population, as are many investigations of rare disease populations. In addition, the MD STAR*net* conducts active case finding and systematic and standardized collection of data over time, which ensures that the data are comparable across each record. This sample is likely the largest reported sample of siblings with DBMD.

This study also has important limitations to recognize. For many of the sibling pairs, neither or only 1 of the siblings has experienced the outcome of interest, which limits conclusions that can be drawn regarding similarity in course. Because the survival analyses relied on the older brother's condition onset age as the predictor, it was necessary to exclude pairs in which the older brother had not experienced the milestone condition, even though the younger brother had. This could potentially bias the results, making the correlation between milestone progression appear greater than it is. Only 1 of 36 sibling pairs was excluded for this reason from the ceased ambulation survival analysis, thus limiting the potential effect of this bias in these results. Three sibling pairs were excluded from the scoliosis analyses and 3 from cardiomyopathy, analyses with already smaller sample sizes. However, because both of these analyses found no significant correlation in sibling's age of progression, no spurious correlations were produced by this bias. It is also important to recognize that improved treatment has resulted in improved outcomes over time, so that siblings who are far apart in age may have different disease patterns as a result of improved treatment. Examination of single treatment factors, such as steroid use, may not capture the collective effects of improved treatment over time. Although loss of ambulation may be hastened by a lower limb fracture, no study subject experienced one in the 6 months before ceased ambulation. Another potential confounding factor for ceased ambulation is obesity; however we were unable to assess BMI reliably in this population, because height measurements were performed infrequently, particularly in those with limited mobility. And finally, because the MD STAR*net* obtains data from existing medical records, the information available for analysis is necessarily limited to what is recorded in those records.

In conclusion, there is substantial variability in the age when younger brothers reach clinical milestones, compared with their older brothers: from 2 years, 3 months earlier to 3 years, 10 months later for scoliosis, 6 years, 9 months earlier to 3 years, 11 months later for ceased ambulation, and 11 years, 11 months earlier to 7 years, 5 months later for cardiomyopathy.

Such differences suggest that the age at which an older sibling reached a milestone is often not helpful for anticipating whether or at what age a younger sibling will reach that same milestone. As a general trend, however, the age at which older brothers ceased ambulation predicted the age when their younger brothers also reached that milestone. For each additional month of ambulation by the older brother, the hazard of ceased ambulation by the younger brother decreased by 4%. These results have implications for trials of therapeutic interventions in DBMD and suggest that large numbers of subjects will likely need to be enrolled to detect significant benefits.

Acknowledgments

We thankfully acknowledge the efforts of the record abstractors, abstract reviewers, and data managers without whom this work would not have been feasible, and we are grateful to the families who participated in this study with MD STAR*net*.

This study was funded by the Centers for Disease Control and Prevention Cooperative Agreement DD000187 for Surveillance and Epidemiologic Research of Duchenne and Becker Muscular Dystrophy. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Abbreviations

DBMD	Duchenne and Becker muscular dystrophy
EF	ejection fraction
FS	fractional shortening
MD STARnet	Muscular Dystrophy Surveillance Tracking and Research Network

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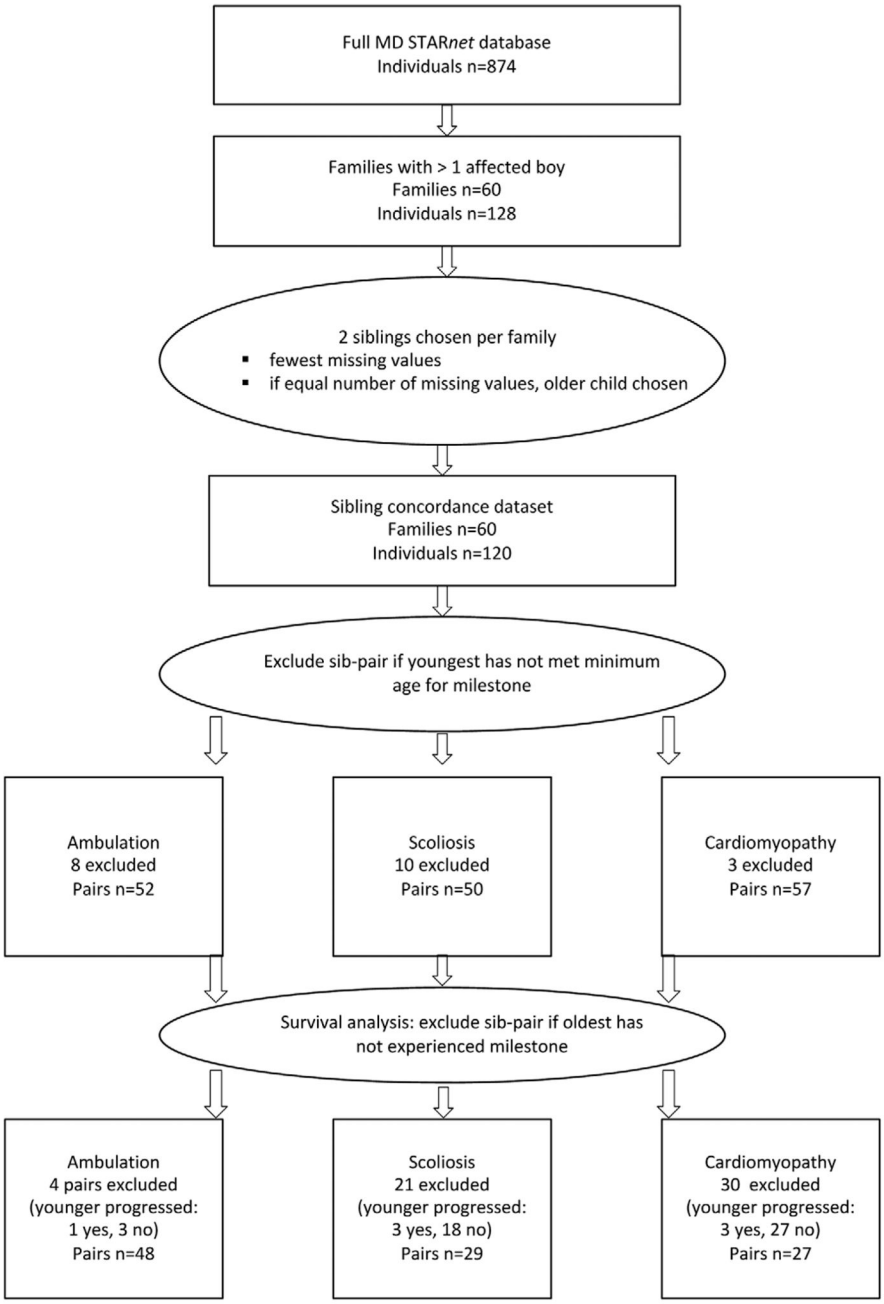

FIGURE 1.
Study population flow chart.

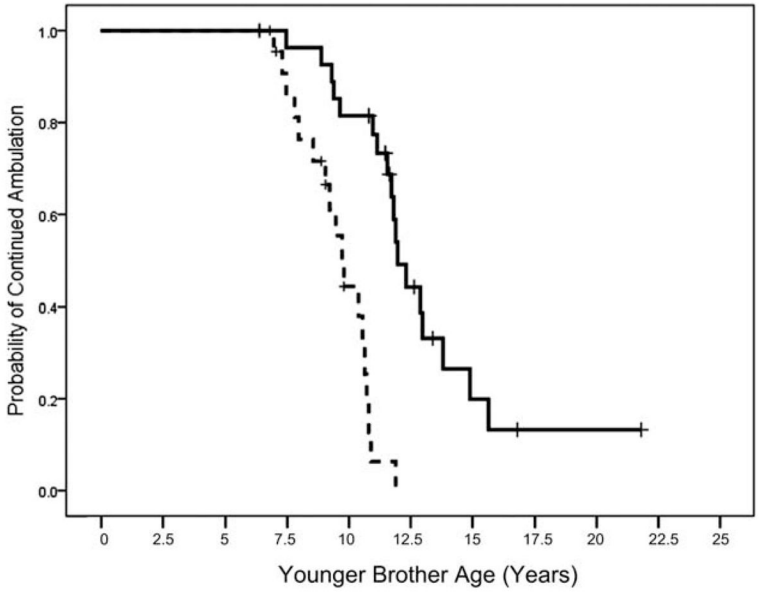

FIGURE 2.

Kaplan-Meier survival analysis demonstrating the relationship between the proportion of younger brothers still ambulatory and whether the older brother ceased ambulation early or late. Probability of younger siblings still being ambulatory by age (years) and when the older brother has ceased ambulation is $P < 0.001$. Solid line, older brother ceased ambulation after the median age of cessation; broken line, older brother ceased ambulation before the median age of cessation; vertical lines, censoring.

Table 1

Number of sibling pairs with concordant progression, discordant progression, or concordant nonprogression for each milestone condition, and minimum age at which a sibling would be at risk for the milestone condition (in months).

Clinical milestone	Minimum risk age (years, months)	No. who reached minimum risk age (pairs)	Concordant progression (pairs)	Discordant progression (pairs)	Concordant nonprogression (pairs)
Ceased ambulation	6, 0	52	35	14	3
Scoliosis ≥ 20°	6, 8	50	9	23	18
Cardiomyopathy	4, 9	57	19	11	27

Table 2

Concordant progression in sibling pairs: Difference in younger sibling's age at clinical milestone onset compared to older sibling's age of onset (in years, months).

Clinical milestone	N (pairs)	Median age difference for onset (years, months)	Minimum (years, months)	Maximum (years, months)
Loss of ambulation	35	0, 2	−6, 9	3, 11
Scoliosis ≥ 20°	9	−0, 8	−2, 3	3, 10
Cardiomyopathy onset	19	−2, 1	−11, 11	7, 5

Table 3

The ratio of the hazard that younger and older brothers reach clinical milestones as a function of age when older brothers reach milestone onset.

Clinical milestone	n	Younger siblings with onset	Younger siblings without onset	Hazard ratio	*P*
Loss of ambulation	48	35	13	0.96	<0.001
Scoliosis ≥ 20°	29	9	20	0.98	0.206
Cardiomyopathy onset	27	19	8	0.99	0.288